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10/039,471	10/19/2001	Mark T. Martin	100391-02030	1031

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

klpatent@kramerlevin.com

Office Action Summary	Application No.	Applicant(s)	
	10/039,471	MARTIN, MARK T.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/11/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,11-17,19,20,27,29,32,34-44 and 46-54* is/are pending in the application.

4a) Of the above claim(s) *34-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,11-17,19,20,27,29,32 and 46-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAIL ED ACTION

Claims 1-3, 11-17, 19-20, 27, 29, 32, 34-44 and 46-54 are pending. Claims 34-44 remained withdrawn.

In response to a previous office action, a non-final action (mailed on 7/11/2008), applicants on 12/11/08 cancel claims 6, 7, 8, 9, 10, 18, 23, 26, 28, 33 and 45; amended claims 1, 17, 19, 20, and 27, and added new claims 46-54.

Applicants' response on 12/11/08 is acknowledged.

Claims 1-3, 11-17, 19-20, 27, 29, 32 and 46-54 are under consideration. Applicants' arguments filed on 12/11/08 have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

35 U.S.C 112 second paragraph Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is unclear in the recitation of "turnover" because the word "turnover" refers to the number of catalytic cycle per unit of time. The claim is reciting the

number of cycles, but does not recite the period of time in which these cycles are accomplished.

35 U.S.C. 112 first paragraph Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 11-17, 19-20, 27, 29, 32 and 46-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained as set forth in the prior Office action, and restated below for applicants' convenience.

Claims 1-3, 11-16 and 46-48 are directed to methods of modifying any TNFalpha, IL-4, IL-6 or VEGFR2 molecule by attaching any sugar or beta-lactam antibiotic type label using any catalytic antibody (CMAB). Claims 17, 19-20, 27, 29, 32 and 49-54 are directed to any catalytic antibody molecule that modify any TNFalpha, IL-4, IL-6 or VEGFR2 type target molecule by attaching any sugar or beta-lactam antibiotic type label.

The specification fails to describe in any fashion the physical and/or chemical properties of any catalytic antibodies. The specification does not

describe any antibody that catalyses a glycosylation reaction between any TNF-alpha, IL-4, IL-6 or VEGFR2 type target molecule and any sugar molecule. These target molecules comprise multiple functional groups, such as, amino group, carboxyl groups, hydroxyl group. An antibody that catalyses a glycosylation or acylation reaction between a functional group of the target molecule and the label molecule depends on transition state of the bond formed between the two functional groups. Production of specific catalytic antibody depends on the structure of the specific transition state analog (section 7, Tewfik et al. from IDS). In most cases, even a single hapten molecule of a transition state analog (for forming or cleaving a bond) elicits multiple antibodies (page 2504, last pargh, Janda et al. from IDS). Yu *et al* (*Ang. Chem. Int. Ed. Engl* 1994, 33, 339-341) studied production of catalytic antibodies having glycosidase activity (glycosylation reaction) for sugar molecule. Yu *et al* teach that mimicking half chair TS for glycosylation reaction is very difficult and after using various TS analogs Yu *et al.* screened 66 antibodies and unable to find any antibodies that shows glycosidase activities (page 340 last paragraph). Therefore, production of catalytic antibodies is dependent on hapten molecule that mimics the transition state analog of the glycosylation reaction. The specification teach that there is a spontaneous reaction between TNF-alpha and glucose molecule (page 37 Table 1) and spontaneous acylation between ampicilin and TNFalpha (page 37, last pargh) and suggests that an antibody would have lower threshold to catalyses the reaction between TNFalpha and sugar molecule or beta-lactam antibiotic. However, the specification does not describe any antibody that catalyses a

glycosylation reaction between any TNFalpha, IL-4, IL-6 or VEGFR2 type target molecule and any sugar molecule. The specification lacks description of any transition state analog that mimic the transition state structure of an acyl or glycosyl transfer reaction between any of TNFalpha, IL-4, IL-6 or VEGFR2 type target molecule and beta-lactam antibiotic or any sugar molecule. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants' are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Applicants' arguments, on pages 10-13 of their amendment, against rejection of claims 1-3, 11-17, 19-20, 27, 29, 32 and 46-54 under 35 U.S.C 112, first paragraph written description requirement are acknowledged. Applicants argue that amended claims now recite catalytic antibodies that attach a specific label (sugar or beta-lactam antibiotic type molecule) to TNFalpha, IL-4, IL-6 or VEGFR2 target *via* non-catalytic glycosylation or acylation reaction and specification possesses the invention. Also, Applicants argue that Example 1 and 2 teach TNF-alpha, IL-4, IL-6 or VEGFR2 target and label molecule comprising sugar or beta-lactam molecule.

Applicants' arguments have been fully considered, but they found un-persuasive. The instant claims recite methods of modifying any TNFalpha, IL-4,

IL-6 or VEGFR2 target molecule by attaching any sugar type label molecule using any catalytic antibody *via* formation of any bond between said target molecule and label. As discuss above neither the specification nor any prior art teach any such catalytic antibody. Generation of catalytic antibody molecule is not routine in the art. An antibody that catalyses a glycosylation or acylation reaction between a functional group of the target molecule and the label molecule depends on transition state of the bond formed between the two functional groups. Bond formation between different functional group of target molecule and functional group of label molecule is dependent on the nature of functional groups. Therefore an antibody catalyzes formation of one type of bond between one specific functional group of a target molecule and functional group of a label molecule will not catalyze the bond formation between another type of functional group of a target molecule and functional group of a label molecule. As previously stated and as stated in the specification, catalytic antibodies are generally made using transition state analogs that mimic the transition state of the reaction to be catalyzed. Some transition state analogs or other hapten will produce catalytic antibodies and some will not, as discussed in earlier action. The instant claims are drawn to attaching any sugar label to any TNFalpha, IL-4, IL-6 or VEGFR2 target molecule using any catalytic antibody. The specification certainly does not teach any hapten that will produce such a catalytic antibody. Therefore, the rejection is maintained that one of ordinary skill in the art reading the instant specification would not conclude that applicant had possession of the claimed invention.

Claims 1-3, 11-17, 19-20, 27, 29, 32 and 46-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for any catalytic antibody molecule capable of catalyzing formation of any bond between any functional group of any TNFalpha, IL-4, IL-6 or VEGFr2 type target molecule and any functional group of any sugar or beta-lactam antibiotic type label molecule and methods of modifying target molecule by attaching said label using said catalytic antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claim(s).

These claims encompass any catalytic antibody molecule capable of catalyzing formation of bond between any functional group of any TNFalpha, IL-4, IL-6 or VEGFr2 type target molecule and any functional group of any sugar or any beta-lactam antibiotic type label molecule and methods of modifying said target molecule by attaching said label using said catalytic antibody. Most TNF-alpha, IL-4, IL-6 or VEGFr2 type target comprises multiple functional groups. Bond formation between different functional group of biological target molecule

and functional group of label molecule is dependent on the nature of functional groups. Therefore an antibody catalyzes formation of one type of bond between one specific functional group of a target molecule and functional group of a label molecule will not catalyze the bond formation between other type functional group of a target molecule and functional group of a label molecule. The specification discloses a few label molecules and few target molecule and suggestion of eliciting catalytic antibodies against them. Even each of these target molecules comprise multiple of various functional groups (various amino, carboxyl, hydroxyl groups). However the applicants have not made and isolated a single catalytic antibody. As explained above the structure of the hapten is very crucial in producing antibody those catalyses a reaction and production of specific catalytic antibody depends on the structure of the specific transition state analog. As for example, Yu *et al* (*Ang. Chem. Int. Ed. Engl* 1994, 33, 339-341) studied production of catalytic antibodies having glycosidase activity (glycosyl-ation reaction) for sugar molecule. The specification teach that there is a spontaneous reaction between TNF-alpha and glucose molecule (page 37 Table 1) and spontaneous acylation between ampicilin and TNFalpha ((page 37, last pargh) and suggests that an antibody would have lower threshold to catalyses the reaction between TNFalpha and sugar molecule or beta-lactam antibiotic. However, the specification does not describe any antibody that catalyses any reaction between any TNF-alpha, IL-4, IL-6 or VEGFR2 type target molecule and any molecule. Yu *et al* teach that mimicking half chair TS for glycosylation reaction is very difficult and after using various TS analogs Yu *et al* screened

66 antibodies and unable to find any antibodies that shows glycosiadase activities (page 340 last paragraph). Therefore, production of catalytic antibodies is dependent on hapten molecule that mimics the transition state analog of the glycosylation reaction. Although specific bond formation between two functional groups of two organic compounds and catalyzing it by catalytic antibodies (CMAB) elicited by known hapten molecule ***in-vitro*** is well known to the skilled artisan; however, finding a suitable transition state analog for the formation of bond between one of the enormous number of functional groups of target biomolecule and functional group of label and producing CMAB for said reaction, and finding which among enormous variants of said MABs (monoclonal antibodies) and said groups as claimed by applicants has desired properties (producing desired CMAB, effecting desired bond formation) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the enormous numbers of functional groups of target biomolecule and functional group of label are suitable for production of CMABs, knowledge of a suitable transition state analog of said bond, and knowledge of which CMABs are suitable to elicit said function (said bond formation). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute **undue** experimentation.

Thus, applicants have <u>not</u> provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any catalytic

antibody molecule capable of catalyzing formation of any bond between any functional group of any TNFalpha, IL-4, IL-6 or VEGFr2 type target molecule by attaching said label using any catalytic antibody. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants' arguments against claims 1-3, 11-17, 19-20, 27, 29, 32 and 46-54, on pages 10-17 of their amendment, against the rejection of the claims under 35 U.S.C 112, first paragraph enablement are acknowledged. Applicants argue that generation of antibody based on skill in the art, detailed description in the specification is not undue. It is true that generation of antibody by immunization with a specific desired antigen is not undue, but as discussed in prior action and above again, generation of catalytic antibody is not routine in the art and as these claims encompass any catalytic antibody molecule catalyzing formation of bond between any functional group of any TNF-alpha, IL-4, IL-6 or VEGFr2 type target molecule and any functional group of any sugar or any beta-lactam antibiotic type label molecule and methods of modifying said target molecule by attaching said label using said catalytic antibody, there require undue experimentation to find out which of any antibody formed will catalyze

bond formation among these diverse group of functional groups of target molecules.

TNF-alpha, IL-4, IL-6 or VEGFr2 type target molecule and label molecules comprise multiple functional groups. Bond formation between different functional group of these target molecules and functional group of label molecule is dependent on the nature of functional groups as well as overall structure. Therefore an antibody catalyzes formation of one type of bond between one specific functional group of a target molecule and functional group of a label molecule will not catalyze the bond formation between other type functional group of a target molecule and functional group of a label molecule. The applicants have not isolated a single catalytic antibody. Furthermore, as explained in detail above the structure of the hapten, the transition state analog, is very crucial in the production of specific catalytic monoclonal antibody (CMAB). Specific bond formation between two functional groups of two organic compounds and catalyzing it by a CMAB elicited by known hapten molecule ***in-vitro*** is well known to the skilled artisan; however, finding a suitable transition state analog for the formation of bond between one of the enormous number of functional groups of target biomolecule and functional group of label and producing desired CMAB for said reaction, and finding which among enormous variants of said MABs produced has desired properties (producing desired CMAB, effecting desired bond formation) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the various functional groups of target biomolecule and functional group of label are suitable

for production of CMABs, knowledge of a suitable transition state analog of said bond, and knowledge of which CMABs are suitable to elicit said function (said bond formation). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. .

Allowable Subject Matter/Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

/Nashaat T. Nashed/
Supervisory Patent Examiner, Art Unit 1652